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THE ACTION OF BASIC LEAD ACETATE ON SOME PHENOLS

and

THE MERCURATION OF β -RESORCYLIC ACID

by

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A THESIS

Submitted to the University of Alberta
in partial fulfilment of the requirements
for the degree of Master of Science.

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ACKNOWLEDGMENTS

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PART I

THE ACTION OF BASIC LEAD ACETATE ON SOME PHENOLS

The study of the chemistry of organo-metallic compounds began as early as the middle of the last century, but it has been developed to a great extent only in more recent years. These compounds have furnished much valuable data which tend to show that there is a great difference in properties between organic metallic derivatives and the inorganic derivatives of the corresponding metals. Also, medical science has urged the preparation of organic derivatives of arsenic, bismuth, antimony, mercury, lead, gold and other metals for therapeutic purposes.

In the treatment of malignant diseases with colloidal lead, W. Blair Bell¹ points out that lead is the most effective metal in treatment of rat sarcoma, and that it almost invariably causes the disappearance of the tumor. A great deal of work must yet be done in regard to the preparation of a real therapeutically active lead substance.

The object of this investigation is the preparation of some phenolic lead compounds. The constitution of these compounds has caused considerable discussion in the recent British chemical and pharmaceutical journals.

1. The Lancet, 210, 537 (1926).

G. A. Medley² discovered that a solution of lead subacetate (Liquor Plumbi Subacetatis Fortis)³ yields a precipitate with an aqueous solution of phenol. He supposed the precipitate to be lead phenoxide, $(C_6H_5O)_2Pb$, which is identical with the compound formed by dissolving lead oxide in hot phenol⁴.

C. S. Gibson and E. Matthews,⁵ of Guy's Hospital Medical School, London, England, investigated this precipitate and suggested that the composition of the compound is best represented by the formula $Pb(OC_6H_5)_2 \cdot Pb(OH)(O_2CCH_3)$. They prepared only three typical compounds for which they show analytical results. These compounds are the ones formed by the action of lead subacetate on an aqueous solution of phenol, o-nitrophenol and o-bromophenol. All these substances are only sparingly soluble in such solvents as water, chloroform, alcohol and pure olive oil. On heating they decompose to give a deposit of lead.

E. A. Lum⁶ has also investigated the phenol compound, but maintains the point of view of G. A. Medley, namely, that the precipitate is lead phenoxide. However, in the preparation of this compound all the lead is not precipitated as such, and therefore he suggested the following equation for the reaction:

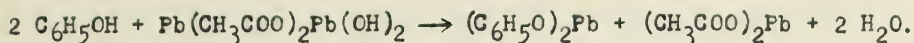
2. Pharm. J., 117, 149 (1926).

3. British Pharmacopoeia, 229, (1914).

4. Calvert, J.Chem.Soc., 18, 69 (1865).

5. J.Chem.Soc., 79, 596 (1928); Pharm.J., 122, 192 (1929).

6. Pharm.J., 122, 149 (1929).



In another paper, E. A. Lum⁷ has changed his point of view, but still not in accordance with Gibson and Matthews, and has given the following equations: $\text{Pb}(\text{OH})_2\text{Pb}(\text{OOCCH}_3)_2 + 2 \text{ C}_6\text{H}_5\text{OH} \rightarrow (\text{C}_6\text{H}_5\text{O})_2\text{Pb} \cdot \text{Pb}(\text{OH})(\text{OOCCH}_3) + \text{CH}_3\text{COOH} + \text{H}_2\text{O}$. The acetic acid is then supposed to react with the second part of the molecule, namely, $\text{Pb}(\text{OH})_2$ to give lead acetate. $\text{Pb}(\text{OH})_2 + 2 \text{ CH}_3\text{COOH} \rightarrow 2 \text{ H}_2\text{O} + \text{Pb}(\text{OOCCH}_3)_2$.

E. Matthews⁸ has given an alternative explanation of the reaction, which is: $3 \text{ Pb}(\text{OH}) \cdot (\text{OOCCH}_3) + 2 \text{ ROH} \rightarrow \text{Pb}(\text{OH}) \cdot (\text{OOCCH}_3) \cdot \text{Pb}(\text{OR})_2 + \text{Pb}(\text{OOCCH}_3)_2 + 2 \text{ H}_2\text{O}$.

It has been attempted in this investigation to determine, as far as possible, the best formula which would represent the product formed when an aqueous solution of lead subacetate reacts with an aqueous solution of a phenol. The work has been rendered quite difficult, due to several reasons. Probably the greatest obstacle has been the fact that these compounds are insoluble and therefore cannot be purified by crystallization.

It has been necessary to carry out analyses on materials, leaving out the essential step of purification. Moreover, many phenolic compounds are readily oxidized by the air and also by the basic lead acetate. Last of all, it has been necessary to

7. Pharm. J., 122, 251 (1929).

8. Pharm. J., 122, 297 (1929).

prepare these compounds, filter them, wash them and dry them in an atmosphere free from carbon dioxide.

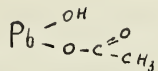
EXPERIMENTAL PART

The basic lead acetate was prepared by shaking mechanically for ten hours 300 g. (1 mole) of $\text{Pb}(\text{O}_2\text{CCH}_3)_2 \cdot 3 \text{H}_2\text{O}$, 175 g. (1 mole) of PbO , and 750 cc. of water. It was then filtered, whereupon a considerable quantity of white precipitate was left on the filter paper. The filtrate was made up to one litre and kept in and delivered from an apparatus similar to that employed for aqueous solutions of barium hydroxide.

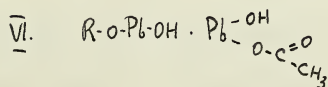
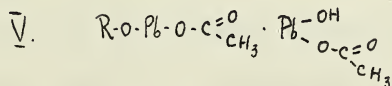
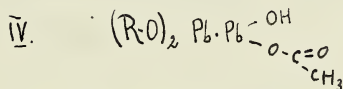
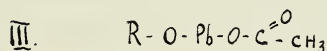
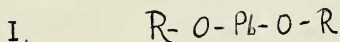
In order to determine the molecular ratio of lead hydroxide to lead acetate in this solution, the amount of lead in 5 cc. of the solution was found to correspond to 2.0871 g. of PbSO_4 . The amount of acetic acid in 5 cc. of the same solution was found to correspond to 72.0 cc. of .1N NaOH. The acetic acid was determined by steam distilling 5 cc. of the solution with an excess of phosphoric acid. The distillate was then titrated according to the regular procedure. Using the above data, the molecular proportion of lead hydroxide to lead acetate in the solution was found to be 1.00:1.04. It might be added here that this is a much better way of determining the composition of the basic lead acetate solution than the various methods described by

Gibson and Matthews.⁹

It is obvious that if the constitution of the basic lead acetate is



then when a phenol reacts with an aqueous solution of basic lead acetate, there is the possibility of the formation of a compound of any one of the following structures. R indicates an aryl or substituted aryl group.



The possibility of different compounds might be even greater than this. It will be noticed that the number of phenolic hydroxyl groups to atoms of lead in formula I is 2:1; in formulas II, III and IV it is 1:1; and in formulas V and VI it is 1:2. As a result, phenolic lead compounds might be grouped into three classes, depending upon this ratio. It has been found, as the following analytical data show, that the lead compounds of phenols do tend to be compounds in which the ratio is 1:1. Especially do they fit in with a structure represented by formula IV, as Gibson and Matthews¹⁰ have shown.

In order to determine whether the apparatus and experimental conditions were comparable to those of Gibson and Matthews, the compounds of phenol and o-nitrophenol were prepared. The following results indicate that such was the case.

The method for the preparation of the phenol lead compound will be described in detail. The remaining compounds were prepared similarly.

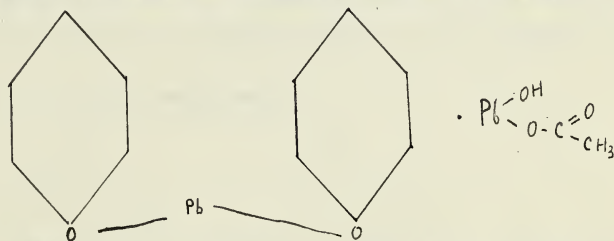
Phenol compound. Phenol (6 g.) dissolved in water (150 cc.) at 20°, was allowed to react with 40 cc. of the basic lead acetate solution. An immediate white precipitate was formed. The precipitate was filtered off by suction and washed with approximately 200 cc. of water at 20°. All operations were

10. J. Chem. Soc., 79, 596 (1928).

carried out in an atmosphere free from CO_2 . The water used was also free from CO_2 . The phenol lead compound was dried in a vacuum desiccator over P_2O_5 . It was a white micro-crystalline powder, which began to melt at about 80° (decomp.) and then charred, leaving a deposit of lead and some lead oxide.

Anal. Calcd. for $\text{C}_{14}\text{H}_{14}\text{O}_5\text{Pb}_2$: Pb, 61.25. Found: 61.66, 61.80, 61.50, 61.50, 61.71, 61.70, 61.80, 60.9, 60.3.

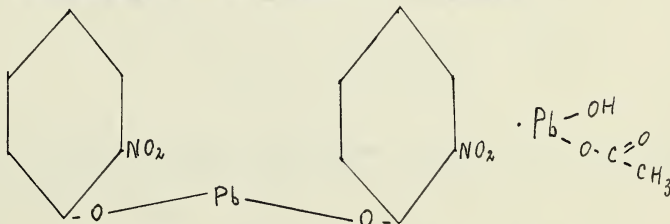
This indicates a compound of the following structure:



o-Nitrophenol compound. This was obtained as an orange crystalline powder.

Anal. Calcd. for $\text{C}_{14}\text{H}_{12}\text{O}_9\text{N}_2\text{Pb}_2$: Pb, 54.05. Found: 53.60, 54.18, 54.58, 54.74.

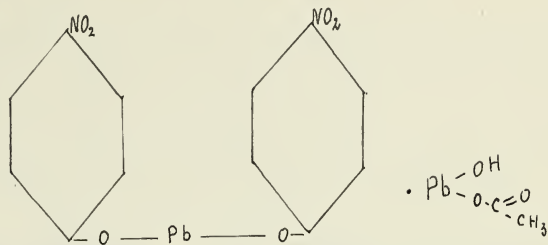
This suggests a compound of the structure:



p-Nitrophenol compound. This material was precipitated as a light yellow crystalline powder.

Anal. Calcd. for $\text{C}_{14}\text{H}_{12}\text{O}_9\text{N}_2\text{Pb}_2$: Pb, 54.05. Found: 54.40, 55.15, 55.37.

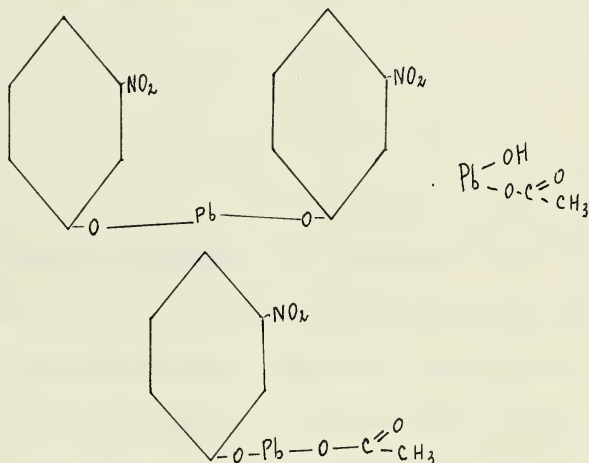
It is suggested that this compound is best represented by the formula:



m-Nitrophenol compound. This was also a yellow compound.

Anal. Calcd. for $\text{C}_{14}\text{H}_{22}\text{O}_9\text{N}_2\text{Pb}_2$: Pb, 54.05. Found: 52.7.

This seems to indicate that we are possibly dealing with a mixture of the two compounds:



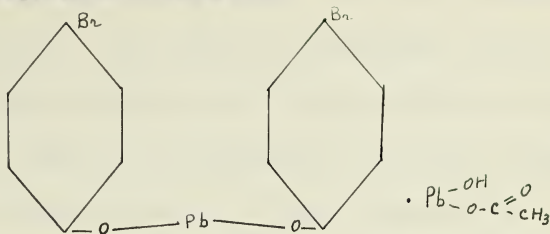
and

The first compound contains 54.05 per cent of lead, the second 51.26 per cent of lead.

p-Bromophenol compound. This compound was precipitated as a white solid.

Anal. Calcd. for $\text{C}_{14}\text{H}_{12}\text{O}_5\text{Br}_2\text{Pb}_2$: Pb, 49.6. Found: 48.40, 48.50.

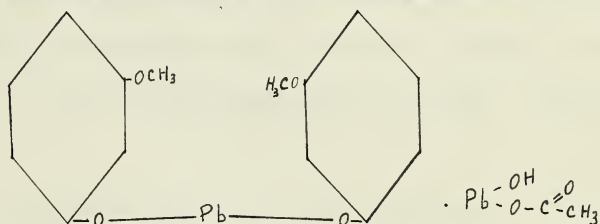
The suggested formula is:



Guaiacol compound. This compound was obtained as a voluminous white precipitate.

Anal. Calcd. for $C_{16}H_{18}O_7Pb_2$: Pb, 56.27. Found: 56.54, 55.96.

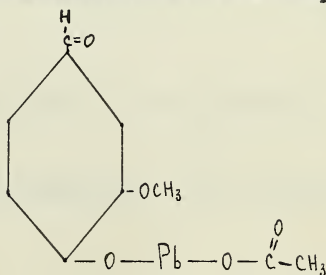
The probable structure of this compound is:

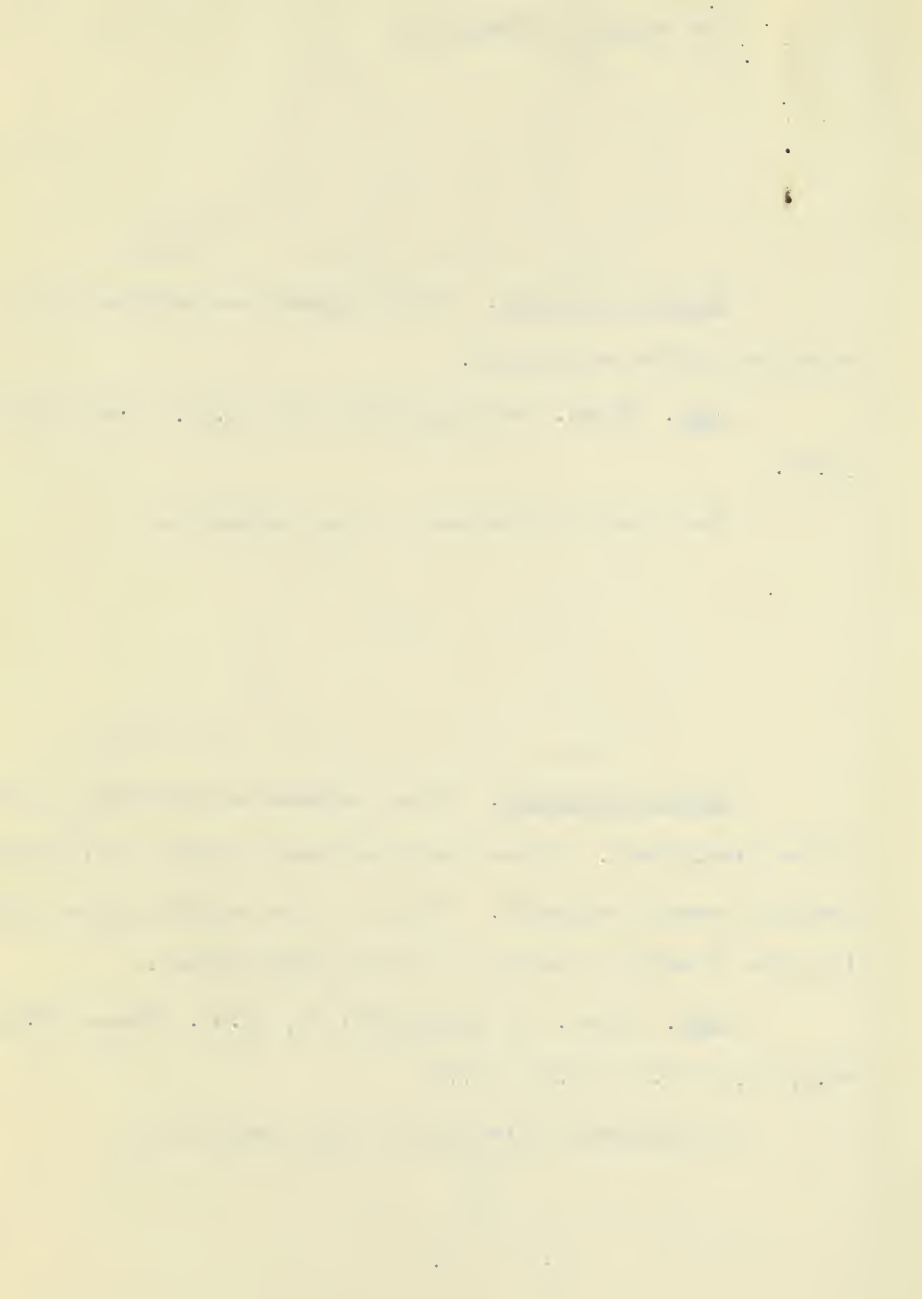


Vanillin compound. This compound was obtained as a light yellow precipitate. It has the appearance of being a very stable compound towards oxidation. This is to be expected since vanillin, in spite of being a phenol, is a very stable phenol.

Anal. Calcd. for $C_{10}H_{10}O_5Pb$: Pb, 49.67. Found: 48.9, 48.5, 48.5, 49.21, 49.92, 49.71.

The suggested structure for this compound is:

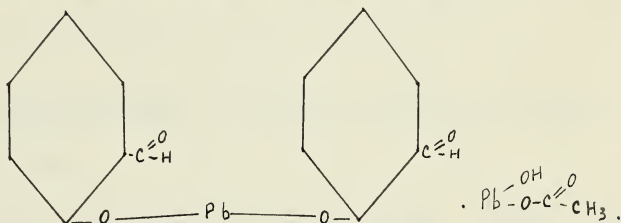




Salicyl aldehyde compound. This was obtained as a light yellow precipitate. The amount of precipitate was not very large, owing to the slight solubility of salicyl aldehyde in water.

Anal. Calcd. for $C_{16}H_{14}O_7Pb_2$: Pb, 56.57. Found: 55.10.

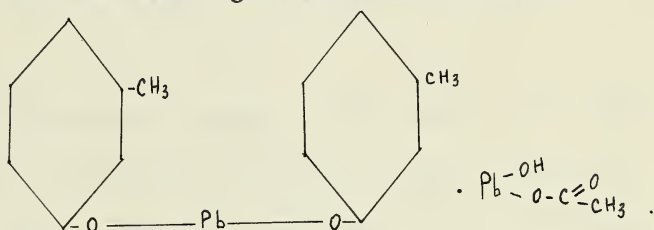
The probable structure of this compound is:



Meta cresol compound. This compound was obtained as a voluminous white precipitate which darkened a little on standing.

Anal. Calcd. for $C_{16}H_{18}O_5Pb_2$: Pb, 58.82. Found: 57.90, 58.20.

This indicates again the usual structure:



Para cresol compound. It had similar properties to those of the above.

Anal. Calcd. for $C_{16}H_{18}O_5Pb_2$: Pb, 58.82. Found: 57.95, 58.32.

The suggested formula is also similar to the one above.

Phloroglucinol compound. The precipitate in this case was a light grey one.

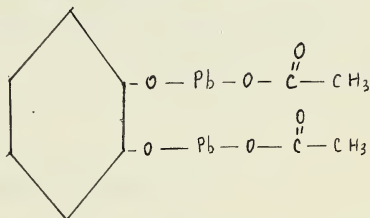
Anal. Calcd. for $C_{18}H_{18}O_{15}Pb_6$: Pb, 72.40. Found: 73.3, 73.2, 73.13, 73.04.

These results fit in with the regular structure given by Gibson and Matthews. However, no attempt has been made to write a graphic formula, owing to the meta positions of the phenolic hydroxyl groups.

Pyrocatechol compound. This was formed as a creamy, voluminous precipitate.

Anal. Calcd. for $C_{10}H_{10}O_6Pb_2$: Pb, 64.71. Found: 65.37, 65.51, 65.40, 65.54, 65.56, 65.20.

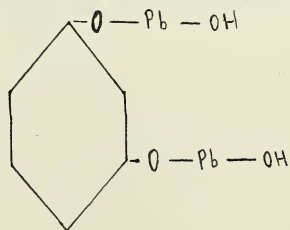
The suggested structure is:



Resorcinol compound. This compound came down at first as a white precipitate, but it soon turned a grey color.

Anal. Calcd. for $C_6H_6O_4Pb_2$: Pb, 74.48. Found: 73.60, 73.80, 73.32, 74.48, 74.28, 73.57, 74.22, 73.89, 73.78, 74.29, 73.47.

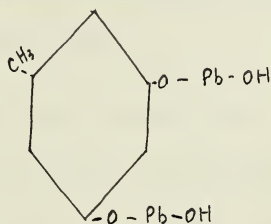
The above results indicate the structure:



Orcinol compound. This compound was formed at first as a white precipitate, but also became dark grey in a very short time.

Anal. Calcd. for $C_7H_8O_4Pb_2$: Pb, 72.70. Found: 73.50, 73.36.

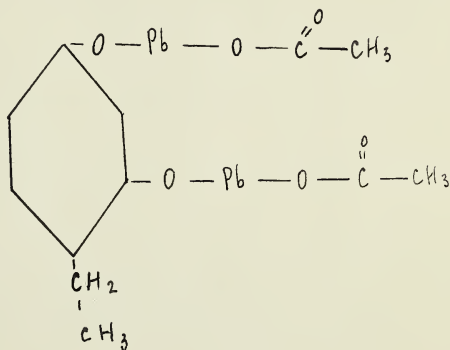
The suggested structure is:



Ethyl resorcinol compound. This compound, which was at first white, soon became light brown in color.

Anal. Calcd. for $C_{12}H_{14}O_6Pb_2$: Pb, 61.99. Found: 61.59, 61.43, 62.39, 62.71.

The suggested structure is:



SUMMARY

1. The lead compounds of the following phenols have been prepared and analyzed: phenol, o-nitrophenol, m-nitrophenol, p-nitrophenol, p-bromophenol, guaiacol, vanillin, orcinol, ortho cresol, meta cresol, salicylaldehyde, resorcinol, ethyl resorcinol, phloroglucinol, pyrocatechol.

2. In every case the analysis for lead indicates a compound in which the ratio of the number of lead atoms to the phenolic hydroxyls is 1:1. In the majority of cases the suggested structure is similar to that of Gibson's structure for the lead phenol compound.

PART II

THE MERCURATION OF β -RESORCYLIC ACID

Considerable work has been done on the mercuration of resorcinol and various derivatives of resorcinol. However, nothing has been recorded in the literature on the mercuration of the carboxylic acid derivatives of resorcinol. For this reason, and also because resorcinol compounds¹ have definite therapeutic values, it was considered advisable to study the mercuration of β -resorcylic acid, which is a carboxylic acid derivative of resorcinol.

The formulas given are only tentative ones. In order to prove absolutely the structures of the compounds prepared, it is necessary to convert these compounds into the corresponding iodine derivatives of which the structures are known. It is almost certain, however, that the mercury groups are in ortho and para positions, that is, in positions 2 and 6, to the phenolic hydroxyl groups in the dimercurated β -resorcylic acid, and in either one of these two positions in the monomercurated β -resorcylic acid. An orientation of the mercury meta to phenolic hydroxyl is entirely improbable.²

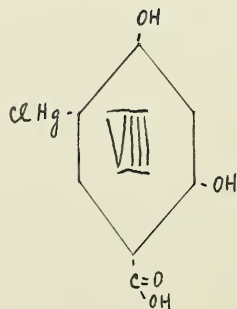
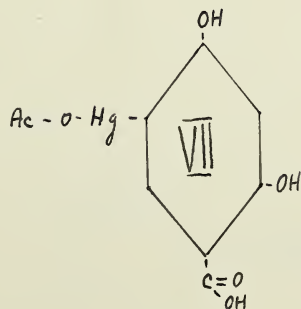
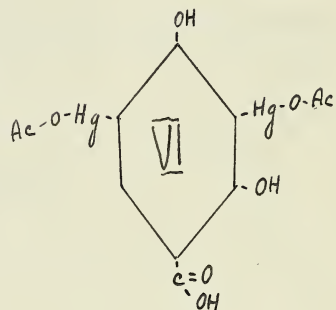
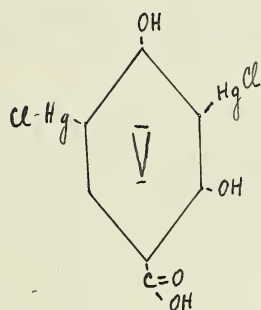
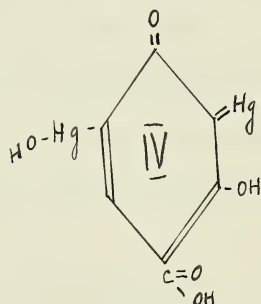
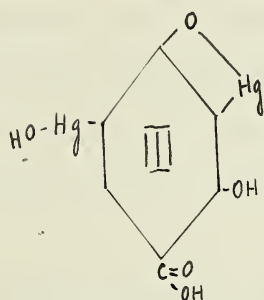
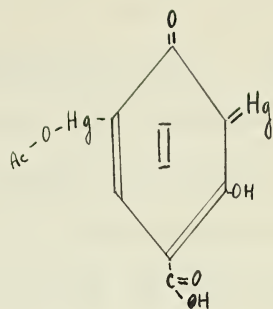
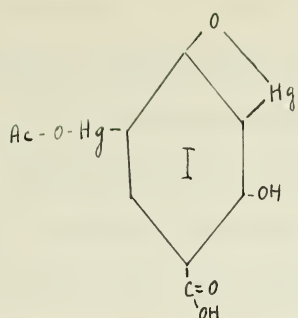
β -Resorcylic acid very readily forms a dimercurated derivative when one molecular proportion of the acid reacts with

-
1. Johnson and Lane, J.A.C.S., 43, 348 (1921)
Leonard, J. Urol., 12, 585 (1924)
 2. Kharasch, J.A.C.S., 43, 1203 (1921)

two molecular proportions of mercuric acetate in a mixture of hot alcohol and acetic acid. Very good indications have also been obtained that the monomercurated derivative is formed when the molecular ratio of the acid to mercuric acetate is 2:1. Very recently Fox and Whitmore³ have found that certain organic compounds can be mercurated in alkaline solution, while other compounds of very similar structure cannot. In this work it has been found that β -resorcylic acid can be mercurated in alkaline solution.

In this piece of investigation, as in the first one, it has been necessary to work under certain difficulties. The chief difficulty has been the fact that these mercury derivatives are very slightly soluble or not at all in the ordinary organic solvents. It has been necessary, therefore, to work with very pure starting materials, and then analyze the unpurified products. In the case of the dichlorodimercuri- β -resorcylic acid, which was slightly soluble in hot alcohol, crystallization gave only a gelatinous precipitate, which then was very difficult to dry. Therefore, even in this case, purification was not attempted. Again there was the difficulty of anhydride formation when the acetoxymercuri- β -resorcylic acids were concerned. The anhydride group always tends to be formed by the elimination of acetic acid between the phenolic hydroxyl and the acetoxymercuri group ortho to it.

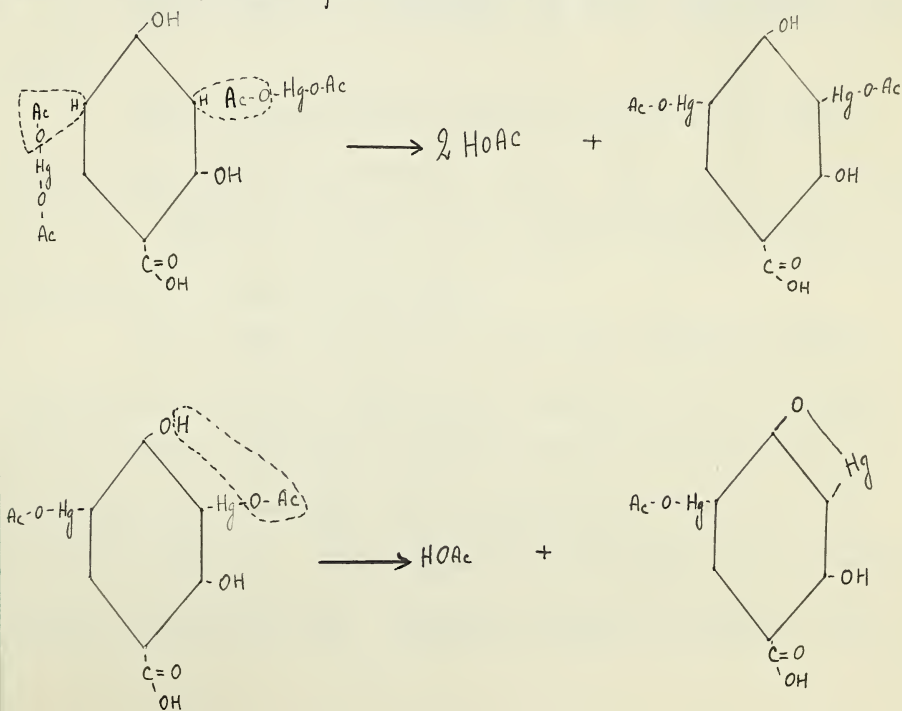
3. Fox and Whitmore, J.A.C.S., 51, 2196 (1929)



The mercury determinations were carried out by decomposing the mercury compound with fuming nitric acid. The inorganic mercury in the resulting solution was then determined as mercuric sulfide. It was impossible to determine the acetate content by the regular procedure, because of the interfering decomposition of β -resorcylic acid into carbon dioxide and resorcinol.

Attention here is called to the fact that in the case of the preceding lead compounds we have been dealing with the lead salts of the weakly acidic phenols. Here we are dealing with mercury carbides, that is, there is a direct linkage between mercury and carbon.

A typical reaction, namely, the formation of the anhydro-mercuri-acetoxymercuri- β -resorcylic acid is the following:



EXPERIMENTAL PART

Preparation of the dimercurated derivatives of β -resorcylic acid. The β -resorcylic acid used was obtained from the Eastman Kodak Company. It was also made by the Kolbe process from resorcinol and KHCO_3 . Three and eight-tenths g. (0.02 mole) of β -resorcylic acid dissolved in 50 cc. of hot alcohol was added to a boiling solution of 12.72 g. (0.02 mole) of mercuric acetate in 250 cc. of alcohol and 5 cc. of glacial acetic acid. Almost immediately a pale yellow solid separated. It was filtered off by suction immediately and washed with hot alcohol. It was air dried for three days. The yield was 11.6 g. It is insoluble in all ordinary organic solvents.

Anal. Calcd. for $\text{C}_9\text{H}_6\text{O}_6\text{Hg}_2$: Hg, 65.6. Found: 65.6, 66.4, 66.1.

These results indicate that the compound is an anhydro-mercuri-acetoxymercuri- β -resorcylic acid. It is given the structure I or II. Structure II, which is the ortho quinoid structure, accounts for the pale yellow color.

In the above preparation, if a large amount of glacial acetic acid is used and practically no alcohol, or if the experiment as already described is carried out and then followed by a heating on the water bath, a precipitate which is white and not yellow, is obtained. This compound is undoubtedly the di-acetoxymercuri- β -resorcylic acid. However, attempts to obtain it pure

in the air dried condition have so far been unsuccessful.

Anal. Calcd. for $C_{11}H_{10}O_8Hg_2$: Hg, 59.8. Found: 61.7, 61.5.

These results show anhydride formation by the loss of acetic acid. This is a property to be expected. The structure for the di-acetoxymercuri compound is Formula VI.

If either of the two above compounds is carefully dissolved in dilute sodium hydroxide solution, and the solution then made slightly acid with dilute HCl (this must be done carefully and with stirring, since a localized high concentration of hydrochloric acid breaks the carbon-mercury bond), the dichloro-dimercuri- β -resorcylic acid is formed. This is a white gelatinous compound. It was carefully dried in the air oven at 100°.

Anal. Calcd. for $C_7H_4O_4Cl_2Hg_2$: Hg, 64.2. Found: 63.5, 63.5.

The structure for this compound is indicated by Formula V.

In order to show that β -resorcylic acid can be mercurated in alkaline solution, 3.08 (0.02 mole) of the acid was dissolved in sodium hydroxide solution. This was then added to a hot mixture made by adding an excess of sodium hydroxide to a solution of an excess over 0.02 mole of mercuric acetate in water and acetic acid. Some undissolved material was filtered off. Carbon dioxide was then passed through the filtrate, whereupon a brown precipitate of the anhydromercuri-hydroxymercuri- β -resorcylic

acid was obtained. It was washed repeatedly with water by decantation, then filtered by suction and finally very carefully dried in the air oven at 100°.

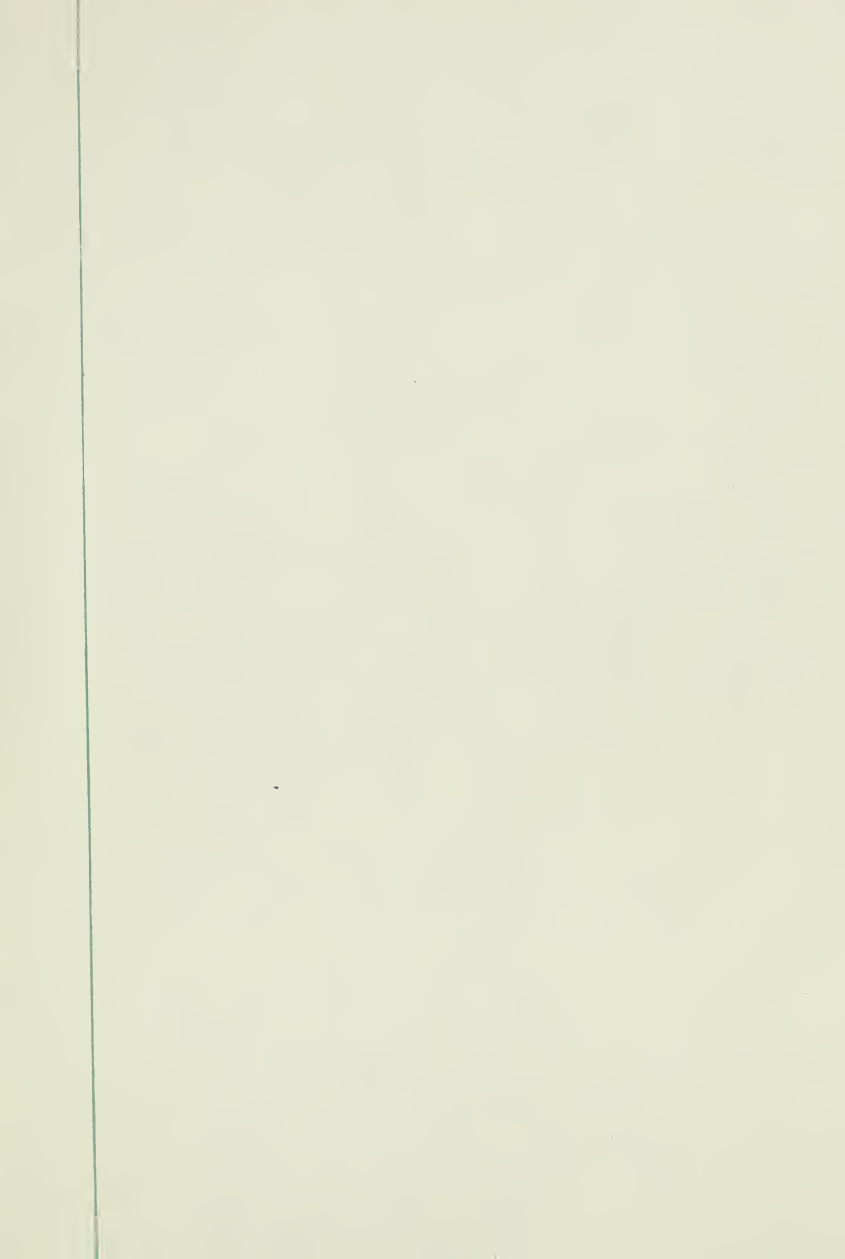
Anal. Calcd. for $C_7H_4O_5Hg_2$: Hg, 70.4. Found: 69.9.

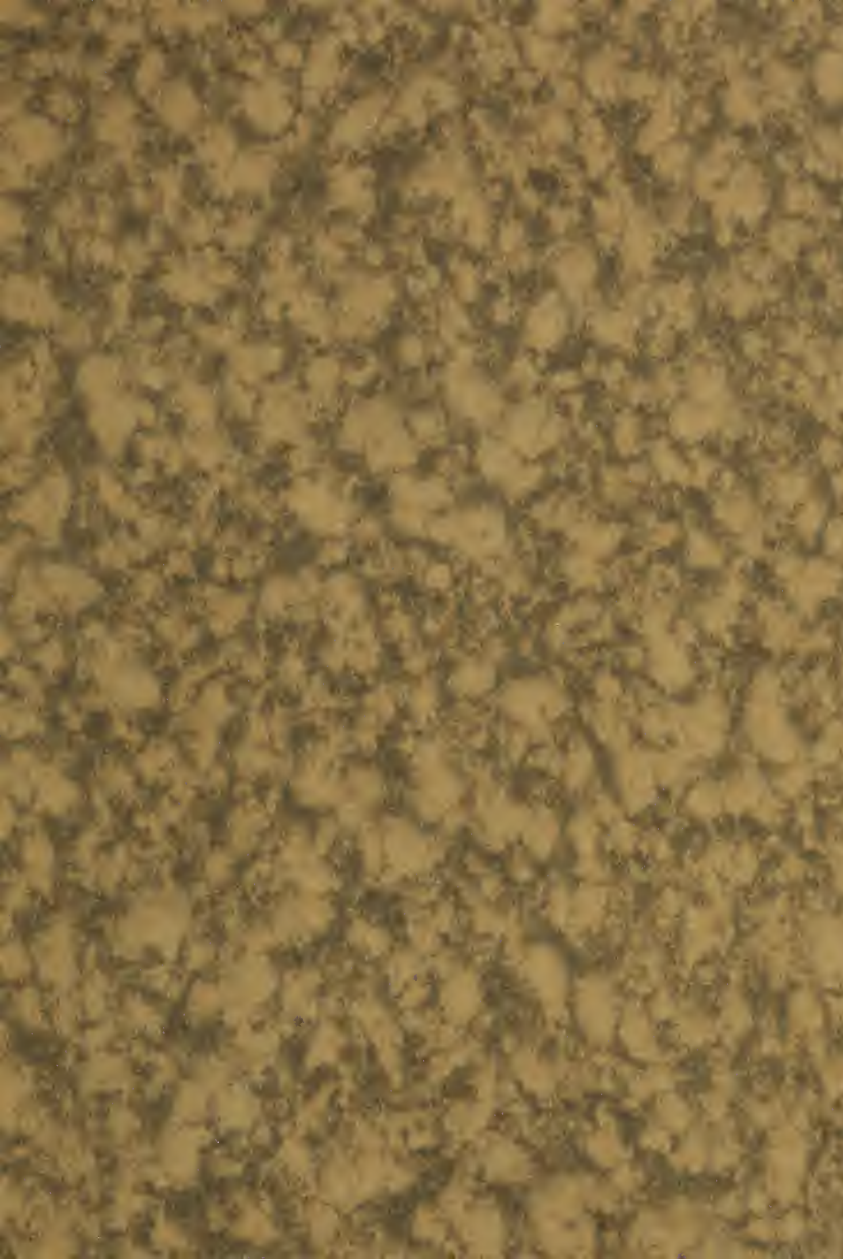
The structure for this compound is represented by Formula III or IV.

In order to obtain a monomercurated β -resorcylic acid, one mole of mercuric acetate was added, with heating and stirring, to two moles of β -resorcylic acid in a very small amount of glacial acetic acid. While still hot, the solution was poured into water, whereupon a white solid monoacetoxymercuri compound separated. Or, if the hot solution was poured into a saturated salt solution, a white solid monochloromercuri compound was formed. The mercury results on these compounds are on the average 3 per cent too high and this work is being continued. The structures of these two compounds are respectively VII and VIII.

SUMMARY

1. The mercuration of β -resorcylic acid is described.
2. β -Resorcylic acid is mercurated in alkaline solution.





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